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Chemistry of Organophosphorus Compounds and Production of Organophosphorus Insecticides

At a general meeting of the Department of Chemical Sciences, Academy of Sciences USSR, held on 21 October 1954, Academician A. Ye. Arbuzov told about the work done by the Kazan' Affiliate of the Academy of Sciences USSR on the synthesis of organophosphorus insecticides.

A. Ye. Arbuzov has studied since 1903 problems pertaining to the structure of derivatives of phosphorous acid. One of the most interesting transformations discovered by him is the Arbuzov rearrangement, i. e., the isomerization of esters of phosphorous acid into esters of alkylphosphonic acids. Up to now USSR and foreign chemists have investigated more than 300 cases of this rearrangement. Investigation of a compound which bears a relation to phosphorous acid has resulted in a new and very simple method for obtaining free radicals of the triarylmethyl series. On the basis of the newly discovered reaction, esters of hypophosphoric, pyrophosphorous, and pyrophosphoric acids were prepared for the first time. Subsequently on the basis of the same reaction organophosphorus compounds of new types were synthesized. These compounds proved to be very powerful insecticides.

Beginning with 1946, many new organophosphorus compounds were synthesized at the Kazan' Affiliate. However, the toxic and insecticidal properties of these compounds have not been investigated to a sufficient degree, because it is impossible to produce an adequate assortment of these compounds under laboratory conditions. In order that the problem of the application of organophosphorus compounds in agriculture be solved completely, it is necessary to manufacture them on a semi-plant scale.

Out of many hundreds of compounds synthesized during the past 3-4 years, the best-investigated and most promising are tetraethyl pyrophosphate ("tepf"), tetraethyl dithiopyrophosphate ("ditio"), tetraethyl monothiopyrophosphate ("pirofos"), and octamethyl tetramidopyrophosphate ("oktametil"). Tests carried out with these chemicals, particularly pirofos [pyrophos] and oktametil [oktamethyl], indicated that they are the most effective agents which are available at present for the control of agricultural pests, including the Colorado beetle.

A. Ye. Arbuzov described briefly the methods for preparation of the most active insecticides [of this class]. A very simple method of producing "tepf" has been developed. Out of five synthetic procedures for the preparation of pyrophos, two can be easily adapted to semi-plant production and full-scale production at industrial plants.

Lately, the attention of investigators has been attracted by octamethyl. The Kazan' Affiliate has developed simplified methods for the synthesis of this powerful insecticide, which exerts its activity inside the plant, i. e., has a so-called systemic action. Tests carried out with octamethyl under field condition gave very encouraging results. The affiliate receives many orders for octamethyl, which, of course, it cannot fill.

One must conclude from this that it is necessary to organize the production of at least three of the chemicals mentioned at one of the plants of the Ministry of Chemical Industry USSR, with the view of providing a sufficient supply of them for field tests to be carried out on a large scale in the spring of 1955. (1)

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Uses of Organophosphorus Compounds and the Toxic Effects Produced by Them

One of the 3 isomers of tricresyl phosphate, an ester which is used as a plasticizer, is o-tricresyl phosphate. The ortho-isomer exerts a selective action on the nervous system, producing a specific toxic polyneuritis. The pathological condition due to poisoning with this substance bears the character of a myeloradiculopolyneuritis or of an encephaloradiculopolyneuritis with predominant injury to the fibers of peripheral motor nerves (Drogichina). This poison also affects the blood capillaries and the intestine. It produces a cumulative effect. There is a prolonged latent period prior to paralysis. Some investigators are of the opinion that the changes produced by o-tricresyl phosphate take place in the muscles rather than in the nerves, i. e., that a cereous degeneration of the type described by Walthard and Walthard occurs in the muscles. The para- and meta-isomers are not very poisonous. Dibazol is recommended for the therapy of the effects of poisoning with o-tricresyl phosphate. (2)

Tetraethyl pyrophosphate is used as an agricultural insecticide in the form of vapotone, a mixture containing 20% of tetraethyl pyrophosphate, 30% of bound organic phosphates, and 50% of inert matter. This substance is toxic to animals and humans. A case of human poisoning with it has been described. The symptoms comprised weakness, a feeling of constriction in the chest, nausea, salivation, diarrhea, spasms, severe miosis, and a stunned condition. (3)

Hexaethyl tetraphosphate (bladan) is prepared by reacting triethyl phosphate with phosphorus oxychloride. It has not been isolated in the pure state and may be a mixture of several esters. It is used as an insecticide. The toxic action of this substance is due to the formation of tetraethyl pyrophosphate by hydrolysis. A dose of 2-3.5 mg/kg, on being administered subcutaneously to white mice, kills the animals within a few minutes. (4)

The alkyl esters of fluorophosphoric acid are highly poisonous by reason of the fact that they produce an irreversible inhibition of the enzyme cholinesterase. Those alkyl fluorophosphates which contain a branched alkyl radical (e. g., isopropyl fluorophosphate, diisopropyl fluorophosphate) are particularly toxic. The toxicity drops sharply when the fluorine atom is replaced by OH, OC_2H_5 , SH, or CN. It is also reduced when the fluorine atom is replaced by another halogen, a second atom of fluorine is introduced, or the oxygen in the ester group is replaced with sulfur.

Diisopropyl fluorophosphate is used as an insecticide and as a disinfectant. It is prepared by reacting phosphorus trichloride with isopropyl alcohol dissolved in carbon tetrachloride. The crude reaction product is chlorinated and then heated with sodium fluoride. After filtration and evaporation of the carbon tetrachloride, pure diisopropyl fluorophosphate is distilled over.

The syndrome observed after poisoning with diisopropyl fluorophosphate resembles that encountered after poisoning with muscarine or nicotine. The muscarinic action is expressed in persistent miosis, salivation, vomiting, diarrhea, fibrillation of the muscles, and other symptoms, while the nicotinic action results in disturbances of motor coordination, excitement, spasms, and subsequent suppression of the respiration. Death ensues as a result of disturbances in the respiration and the circulation. In rabbits the muscarinic effects predominate, while cats exhibit predominantly the symptoms that are typical for nicotinic action.

When human beings are exposed to the action of small doses of diisopropyl fluorophosphate, they develop primarily gastrointestinal symptoms,

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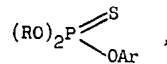
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i. e. lack of appetite, nausea, vomiting, stomach aches, and diarrhea. Persistent miosis continuing for at least a week has been observed following the inhalation of diisopropyl fluorophosphate in a concentration of 0.1 mg/liter for 3 minutes.

To counteract the nicotinic action of diisopropyl fluorophosphate, magnesium sulfate has been used in animal experiments. The muscarinic action was counteracted by administering atropine. The combined administration of 20 mg of magnesium sulfate and 5 mg of atropine per 1 kg of the weight of the animals was found to stop the spasms for 30-60 minutes. Eight hundred mg of magnesium sulfate and 20 mg of atropine per 1 kg of the weight of the animal protected the animals from the toxic action for longer periods than that and increased the rate of survival. (5)

Esters of thiophosphoric acid have the general formula



where R is an aliphatic hydrocarbon radical and Ar an aromatic hydrocarbon radical which may contain different substituents. They are used as insecticides and are very active in this respect. The compounds containing a nitro-group in the para-position of the aromatic radical exhibit the strongest activity. The toxic effects produced by compounds of this class in higher animals are due to an inhibition of cholinesterase for a prolonged period. As a result there is poisoning with the acetylcholine which accumulates in excess quantities in the body. In the course of the pathological process produced by the poisoning there are three stages. The first stage reminds one of poisoning with muscarine. In the second stage symptoms typical for poisoning with nicotine develop in addition to symptoms of the muscarinic type. The third stage is characterized by disturbances of the nervous system which are expressed in headaches, vertigo, insomnia, depression and loss of consciousness (coma). The opinion has been expressed that thiophosphoric acid esters, in addition to exerting cholinesterase inhibitor activity, also suppress the activity of Warburg's respiratory enzyme. Death takes place as a result of a paralysis of respiration.

Dimethyl para-nitrophenylthiophosphate is used as an agricultural insecticide. It is prepared by reacting dimethyl chlorothiophosphate with para-nitrophenolate or para-nitrophenol in the presence of soda. The toxic action of this substance is the same as that of diethyl para-nitrophenylthiophosphate (see below), except that it is less strongly expressed.

Diethyl para-nitrophenylthiophosphate is used as an agricultural insecticide and fungicide under the names of parathion, thiophos, and E 605. It is the active principle of the preparation NIUIF-100. This substance is prepared by interacting diethyl chlorothiophosphate with para-nitrophenolate or para-nitrophenol in the presence of soda.

The toxic effects of diethyl para-nitrophenylthiophosphate (thiophos) in human beings are expressed by headaches, vertigo, sometimes unconsciousness, sharp pains in the abdomen, vomiting, and salivation. These symptoms remind one of the syndrome of a toxic infection, except that lowering of the temperature of the body always occurs in cases of poisoning with thiophos. There is a rapid drop in blood pressure and slowing down of the cardiac activity; the beating of the heart assumes a hollow tone; and edema of the lungs and a rapidly progressing insufficiency of the cardiovascular system may occur. In acute cases of poisoning there is mental depression accompanied by difficulties in thinking and by a slowing down of movements. Subsequently the victim becomes

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unconscious (i. e., a state of coma develops). At this stage there is a complete absence of reflexes. Contraction of muscles and paralysis of the muscles closing the colon and the bladder set in. In case of fatal poisoning, death takes place 6-10 hours after the subject has worked with a solution of the substance. Work with dust containing thiophos results in fatal poisoning more rarely than work with a solution.

Clinical symptoms of poisoning with thiophos are observed when the activity of cholinesterase in the blood drops by more than 30%. A case of poisoning with this substance has been described which was accompanied by a 45% drop of cholinesterase activity in the victim's blood. Nevertheless, the cholinesterase activity returned to normal within 48 hours and the patient recovered completely (Sassi, Med Lavoro, Vol 43, p 210, 1952). A high temperature of the air increases the danger of poisoning with thiophos. Out of 183 cases of poisoning with this substance mentioned in one source, 8 cases were fatal. While poisoning in some of these cases occurred as a result of exposure to thiophos at chemical plants, most of the cases in question were connected with the use of this substance (Descille, Derobert, Albanary, Le Breton, Martin, Arch. Malad. Profess., Vol 12, No 4, 1951, p 27).

In the treatment of the effects of poisoning with thiophos, atropine and magnesium sulfate are used. This treatment is combined with a symptomatic surgery that is in accord with the medical indications.

Shakhbazyan recommends that the maximum permissible concentrations should be set at 0.00001 mg/liter for technical [liquid] thiophos and 0.005 mg/liter (5 mg/cubic meter) for dust containing thiophos (Tesizy Dokladov Vtorogo Vsesoyuznogo Soveshchaniya po Voprosam Promyshlennoy Toksikologii, 4-6 Fevralya 1952, Theses of Reports Presented at the 2d All-Union Conference on Problems of Industrial Toxicology, 4-6 February 1952 - , Academy of Sciences USSR, 1952).

Persons working with thiophos should wear special clothing, rubber gloves, boots made of natural rubber or neoprene, facial masks, and under field conditions special waterproof outer coats ("macintoshes"). When preparations containing this substance are used as insecticides, they must be dyed into bright colors. Containers which are well-sealed must be used. Persons who are employed in the production of thiophos or use it under field conditions must be given special instructions. All types of packing used for thiophos or thiophos dusts must bear an inscription warning the users that the contents are toxic and specifying the precautions which must be taken to prevent poisoning. When this substance is used under field conditions, the cabs of tractors must be hermetically closed and appropriately ventilated. All machines, tanks, containers, and other equipment must be washed after every operation and prior to carrying out any repairs. The special work clothing must be changed frequently. It is essential to remove the work clothing after the work and prior to removing it wash the rubber clothing articles (gloves and boots) in running water. A shower bath must be taken after the work. A weekly medical examination is recommended in order that an accumulation of diethyl para-nitrophenylthiophosphate in the body may be watched for and prevented. In hot weather the working time must be reduced. (6)

Observations carried out by investigators at the Institute of Labor Hygiene and Professional Diseases, Academy of Medical Sciences USSR, on two chemical plant workers engaged in the production of thiophos and affected by a mild form of acute poisoning with this chemical established that the clinical symptoms of intoxication with thiophos added up to a syndrome typical for an asthenic condition (cerebral asthenia). At the same time, phenomena of the dysfunction of the vegetative nervous system were apparent. The observations that had been made led to the conclusion that thiophos is a neurotropic poison which in cases of acute poisoning produces a generalized affliction of

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central nervous system accompanied by disturbances in the functioning of the cortico-subcortical, cerebellar-vestibular, and stem divisions of the brain. In individual cases, irritation of the brain membranes may take place. From the clinical standpoint, a condition is established in which symptoms develop that are similar to those of a toxic encephalopathy or meningo-encephalopathy. According to published data, inhibition of cholinesterase activity also takes place during the acute period of the intoxication. Previously published articles pointed out that poisoning with thiophos resembles intoxication with physostigmine.

The following therapeutic and prophylactic measures should be taken in cases of acute poisoning with thiophos. During the first 1-2 days, when pronounced symptoms of an acute intoxication are apparent, inhalation of oxygen, injections of caffeine, camphor and (intravenously) glucose are indicated. If no contraindications such as a weak pulse and arterial hypotension are present, bloodletting in the amount of 200-300 milliliters should be resorted to. On the second or third day after the onset of the poisoning intravenous injections of glucose in combination with thiamin and ascorbic acid should be begun and soporifics (bromural together with luminal) should be administered. Foreign authors have noted that good results were obtained by administering "sinkostiril," camphor, and atropine.

Prophylactic measures should comprise the use of protective clothing goggles, gas masks, etc. It is essential that the temperature of plant production departments at which thiophos is manufactured should not exceed 25°C. (7)

According to a published article emanating from the Kiev Institute of Labor Hygiene and Occupational Diseases, the September 1953 Plenary Session of the Central Committee, CPSU outlined agricultural measures which include expansion of the production and use of organophosphorus insecticides. One of these insecticides is thiophos a substance that has been synthesized at the Scientific-Research Institute of Fertilizers and Insectofungicides imeni Samoylov. Prior to the use of thiophos under field conditions toxicological investigations were carried out which established that this insecticide is a dangerous poison which, among other things, acts on the central nervous system. Investigations conducted by the Kiev Institute of Labor Hygiene and Occupational Diseases led to the conclusion that spraying with aqueous emulsions of thiophos in agricultural practice is less dangerous than the dispersion of dusts containing thiophos, because the dust remains suspended in the air, with the result that concentrations of the poison which exceed the permissible limits are created. When aqueous emulsions are used, the maximum permissible concentration of thiophos in the air is not exceeded. On the basis of the data obtained in this instance, the maximum permissible concentration of thiophos is assumed to be of the order of 0.05 mg/cubic meter, which corresponds to a concentration of 1% thiophos dust amounting to 5 mg/cubic meter. In practice at 1% dust and 30% concentrated emulsion (to be diluted to the requisite concentration) are used. Experiments on animals established that thiophos has a cumulative effect.

In connection with the application of thiophos as an insecticide, a 5% solution of sodium hydroxide, slacked lime in water or soda should be used for decontamination (8)

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